REMARKS

Claims 7-12 appear in the application. Claims 7 and 8 have been amended to more clearly define the invention within the requirements of 35 U.S.C. §112, ¶1. Claims 10-12 have been cancelled without prejudice or disclaimer of applicants' right to pursue patent protection for the subject matter of those claims in another application. New claim 13 is submitted. Claim 13 is identical in most respects to claim 8 as amended, but states in the preamble that the agent "is capable", rather than "is determined to be capable" of inhibiting fusion, "in" a method, rather than "using" a method. The amendments to claims 7 and 8 and the addition of new claim 13 are all entirely supported by the application as filed. In particular, support may be found, *inter alia*, in applicants' specification at pages 60-64. Thus there is no issue of new matter.

THE "WRITTEN DESCRIPTION" REJECTION UNDER 35 U.S.C. §112

In ¶4 on pages 1-4 of the Office Action, claims 7-12 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen,* 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981)and *In re Wertheim,* 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976)). The Examiner stated that the claims are directed toward methods of inhibiting macrophage-tropic HIV-1 fusion to a CD4+ cell target through the administration of an agent or compound that is specific only for macrophage-tropic isolates or methods of inhibiting T-cell tropic HIV-1 fusion to a CD4+ cell target through the administration of an agent or compounds that is specific only for T-cell tropic isolates. The Examiner stated that in order to practice the

claimed invention, the skilled artisan would require macrophage-tropic-specific and T-cell-tropic-specific inhibitory compounds.

The Examiner stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (citing, e.g., *Vas-Cath, Inc., v. Mahurkar,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116). The Examiner stated that the issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of compounds that are required to practice the claimed methodology. The Examiner stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (citing *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41* U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)). The Examiner stated that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. The Examiner stated that a biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest (citing *In re Bell,* 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993) and *In re Deuel,* 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995)). The Examiner stated that a lack of adequate written description issue also arises if the knowledge

and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process (citing *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995)). The Examiner stated that the court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

The Examiner stated that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The Examiner stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The Examiner stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. The Examiner stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does

not satisfy the written description requirement (citing *Regents of the University of California v. Eli Lilly,* 119 F.3d. 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998) and *In re Wilder,* 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984)). The Examiner stated that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The Examiner stated that the molecular determinants modulating HIV-1 envelope fusion are complex (O'Brien *et al.*, 1990). The Examiner stated that the description provides a generic screening assay for identifying putative macrophage-tropic-specific or T-cell-tropic-specific inhibitors. The Examiner stated that however, this screening assay fails to provide any guidance pertaining to the structure of those compounds that can reasonably be expected to inhibit viral cell fusion. The Examiner stated that the skilled artisan cannot reasonably predict the structure of any given inhibitor. The Examiner stated that moreover, the disclosure fails to provide sufficient guidance pertaining to this point. The Examiner stated that while the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T-cell-tropic isolates. The Examiner stated that the disclosure clearly stated (p.60, first paragraph) that "The culture supernatants from hybridomas PA-3, PA-5, PA-6, and PA-7 inhibited fusion between Hela-env_{JR-FL} and PM1 cells in the RET assay, and also inhibited fusion between Hela-env_{LAI} cells and certain CD4+ target cells (Table 3)." The Examiner stated

that thus, the disclosure fails to identify any suitable agents with the desired properties. The Examiner stated that thus, upon perusal of the disclosure, the skilled artisan would reasonably conclude that applicants were not in possession of a reasonable number of macrophage-tropic or T-cell-tropic-specific inhibitory agents. The Examiner stated that moreover, nothing in the disclosure points the skilled artisan toward any particular class of agents.

The rejection of claims 7-12 based upon an alleged lack of an appropriate written description in applicants' specification of the invention recited by the presently amended claims is respectfully traversed. Nevertheless, without conceding the validity of the Examiner's arguments concerning this issue, applicants have amended independent claim 7 as well as claim 8 which depends from claim 7, to more closely align the recitation of the invention contained in these claims with the written description of the invention contained in the present specification. As explained below, claims 7 and 8 as amended, and claim 9 which also depends from claim 7, now meet the "written description" requirements of §112, first paragraph. New claim 13, which as noted above closely tracks the language of (amended) claim 8, also meets the §112 written description requirements for the same reasons as claims 7-9. Claims 10-12 have been cancelled without prejudice or disclaimer, and thus the §112 rejection of those claims is moot.

Claim 7, i.e., the sole independent claim remaining in the application, is directed to a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1. As presently amended, the claim recites a method

comprising contacting the CD4+ cell with an agent which is (1) capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but (2) not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, so as to thereby inhibit the fusion of the macrophage-tropic primary isolate of HIV-1 to the CD4+ cell. Claim 7 as amended specifically recites subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that at the time the application was filed, that the inventors had possession of the invention as now claimed. In particular, the method recited in amended claim 7 involves, as noted above, contacting a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1 with an agent which is:

(1) capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell; and

(2) not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell,

so as to thereby inhibit the fusion of a macrophage-tropic primary isolate of HIV-1 to the CD4+ cell.

The Examiner's attention is respectfully directed to Table 3 on page 61 of applicants' specification, as well as to the accompanying discussion of the Table on specification page 60. Table 3 characterizes four novel monoclonal antibodies which meet the requirements of claim 7 as presently written. That is, as discussed at page 60, hybridomas against PM1 cells were generated and the supernatants from those hybridomas were screened in the RET assay (as recited, e.g., in applicants' claims 8 and 13) to identify hybridomas which secrete antibodies capable of inhibiting fusion between HeLa-env_{JR-F1} and PM1 cells, i.e., as required by amended claim 7. Table 3 on page 61 clearly shows that the novel monoclonal antibodies PA-3, PA-5, PA-6 and PA-7 respectively prevented 85.3%, 96.3%, 92% and 67% of fusion

between HeLa-env_{JR-FL} and PM1 cells.

Furthermore, these same agents, i.e., antibodies PA-3, PA-5, PA-6 and PA-7 had essentially no inhibitory effect on the fusion between HeLa-env_{LAI} and HeLa-CD4 cells, i.e., fully in accordance with the recitation in amended claim 7. As shown in Table 3, the respective inhibition percentages achieved with the antibodies of the present invention with regard to the fusion of the T cell-tropic isolate of HIV to HeLa-CD4 cells was 0%, 0%, 7.7% and 0%. Clearly, therefore, applicants' antibodies fulfill the second aspect of the invention recited in claim 7, i.e., they are essentially not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Thus, the antibodies described in Table 3 are specific examples of agents which operate according to the invention now recited in the claims as presently amended. Therefore, by virtue of the provision of such working examples, the invention is not described solely in terms of a method of its making coupled with its function, wherein there is no art-recognized correlation or relationship between the structure of the invention and its function, as argued by the Examiner on page 2, lines 19-23 of the Office Action.

Applicants submit that the basis of the Examiner's written description rejection under §112 is no longer relevant and is thus moot in light of the amendments to the claims, particularly to claim 7. Applicants have replaced the original language of claim 7 concerning the use of an agent (1) capable of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1, but (2) not capable of inhibiting fusion of a T cell-tropic isolate of HIV-1 to a CD4+ cell susceptible to infection by a T cell-tropic isolate of HIV-1, with significantly more specific language, which is clearly described in the

specification in such a way as to reasonably convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

In the Office Action, the Examiner additionally stated (on page 2, lines 11-13) that the issue is whether the original application provides adequate support for the broadly claimed genus (i.e., requiring macrophage-tropic-specific and T cell-tropic-specific inhibitory compounds) of compounds that are required to practice the claimed methodology. As noted above, however, the amendments to claim 7 have resulted in a more precisely claimed invention in that the terms "macrophage-tropic primary isolate" and "T cell-tropic isolate" have been deleted from the recitation of the method in favor of alternate language as described above which is clearly supported by the written description of the invention in the specification as filed.

The Examiner went on to state at page 4 of the Office Action that while the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6 and PA-7) that are capable of mediating envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T cell-tropic isolates. The Examiner stated that thus the disclosure fails to identify any suitable agents with the desired properties, and that upon perusal of the disclosure; the skilled artisan would reasonably conclude that applicants were not in possession of a reasonable number of macrophage-tropic or T cell-tropic specific inhibitory agents. Applicants respectfully traverse these statements since as noted they have deleted the recitation of a "macrophage-tropic primary isolate of HIV-1" and "T-cell tropic isolate of HIV-1" from the method steps recited in claim 7. Claims 10-12, directed to a method of inhibiting fusion of a T cell-tropic isolate of

HIV-1 to a CD4+ cell susceptible to infection by a T cell-tropic isolate of HIV-1 have, moreover, been cancelled from the application (without prejudice or disclaimer). The claims remaining in the application, as amended, are thus all directed to methods of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 susceptible to infection by a macrophage-tropic primary isolate of HIV-1 wherein the method comprises contacting the CD4+ cell with an agent wherein the agent is (1) capable of inhibiting fusion of HeLa-envJR-F1 to a PM1 cell, but is (2) not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Such agents are clearly disclosed in Table 3 found in applicants' specification on page 61 and in the accompanying descriptive text. For the reasons above, therefore, applicants contend that claim 7, as amended, clearly recites subject matter described in the specification in a manner which reasonably conveys to the skilled artisan that the inventors, at the time of filing the application, had possession of the invention as now recited in the claims. Further, claims 8 and 9, and new claim 13 which also depends from claim 7, each contain all of the recitations of claim 7 due to their dependency on that claim and thus these additional claims also meet the written description requirements of §112 for the same reason as claim 7. The Examiner is therefore respectfully requested to reconsider and withdraw the written description rejection of claims 7-12.

THE "ENABLEMENT" REJECTION UNDER 35 U.S.C. §112

In ¶5 on pages 4-6 of the Office Action, claims 7-12 are rejected under 35 U.S.C. ¶112, first paragraph, on the basis that the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner stated that the claimed invention

is directed toward methods of inhibiting macrophage-tropic HIV-1 fusion to a CD4+ cell target through the administration of an agent or compound that is specific only for macrophage-tropic isolates, or methods of inhibiting T-cell tropic HIV-1 fusion to a CD4+ cell target through the administration of an agent or compound that is specific only for T-cell tropic isolates.

The Examiner stated that the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands,* 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The Examiner stated that the courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims (citing *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965)). The Examiner stated that the disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) the disclosure fails to provide adequate guidance pertaining to the molecular determinants that are specific to macrophage-tropic envelope-mediated cell fusion and T-cell-tropic envelope-mediated cell fusion. The Examiner stated that rational drug development requires knowledge of the molecular determinants that are specific to each type of virus. The Examiner stated that this would provide a starting point for the skilled artisan to begin testing compounds in the hope of identifying something useful. The Examiner stated that however, the disclosure fails to provide any guidance pertaining to this consideration. The Examiner

stated that moreover, the disclosure fails to provide a reproducible method for identifying putative inhibitors. The Examiner stated that while a fusion assay is provided in the specification, the skilled artisan cannot reasonably predict which compounds or agents will function in the desired manner.

2) The Examiner stated that the disclosure fails to provide adequate guidance pertaining to the structural requirements of any given inhibitor. The Examiner stated that the disclosure fails to describe any particular class of compounds that can reasonably be expected to function in the desired manner. The Examiner stated that absent any guidance containing the structure of said compounds, an undue invitation to further experimentation has been extended to the skilled artisan.

3) The Examiner stated that the claims are of considerable breadth and encompass an inordinate number of compounds. The Examiner stated that however, as noted *supra*, the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating macrophage-tropic-specific and T cell-tropic-specific fusion interactions. The Examiner stated that the disclosure also fails to provide any guidance pertaining to the structure of any given inhibitory agent. The Examiner stated that thus, the specification clearly fails to support the breadth of the claimed invention.

4) The Examiner stated that the disclosure fails to provide any working embodiments. The Examiner stated that considering the breadth of the claimed invention, a representative number of working embodiments would be required. The Examiner stated that however, the specification is deficient in this regard. The Examiner stated that moreover, the disclosure clearly illustrates the problems associated with identifying specific inhibitors

wherein it was reported (p. 60, first paragraph) that "The culture supernatants from hybridomas PA-3, PA-5, PA-6, and PA-7 inhibited fusion between Hela-env_{JR-FL} and PM1 cells in the RET assay, and also inhibited fusion between Hela-env_{LAI} cells and certain CD4+ target cells (Table 3)."

The Examiner stated that therefore, when all the aforementioned factors are considered *in toto,* it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Claims 10-12 have been cancelled from the application without prejudice or disclaimer and thus the enablement rejection of these claims is moot. As to claims 7-9 (and new claim 13), applicants submit for the reasons which follow that their specification readily enables one of ordinary skill in this art to both make and use the invention as now recited in the (amended) claims.

While not conceding the validity of the Examiner's position, applicants have amended independent claim 7 as noted above to delete therefrom the recitations that the agent used in the method of the invention is (1) capable of inhibiting fusion of "a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1", but (2) not capable of inhibiting fusion of "a T cell-tropic isolate of HIV-1 to a CD4+ cell susceptible to infection susceptible to a T cell-tropic isolate of HIV-1." In its amended form, the claim now recites that the agent is (1) capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but (2) not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, which language much more closely tracks the written description of the invention in applicants' specification.

For the claimed invention to be enabled, the specification must teach one of ordinary skill in the relevant art how to make and use the invention. Page 60 of applicants' specification teaches that (1) the resonance energy transfer (RET) assay described in the specification can be used to screen antibodies capable of inhibiting HIV-1 envelope-glycoprotein- mediated membrane fusion and (2) hybridomas against PM1 cells were generated and the supernatants from these hybridomas were screened in the RET assay to identify hybridomas capable of inhibiting fusion between HeLa-env_{JR-F1} and PM1 cells. Moreover, as demonstrated by the experimental results set forth in Table 3, the culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 clearly had a strong inhibitory effect on such fusion between HeLa-env_{JR-FL} and PM1 cells. These novel monoclonal antibodies, however, were <u>not capable</u> of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell (see Table 3), as is specifically recited in claim 7. The antibodies obtained from the supernatants of hybridomas PA-3, PA-5, PA-6 and PA-7 are thus four <u>working embodiments</u> of the invention as now claimed.

Applicants respectfully traverse the position taken by the Examiner in ¶2 on page 6 of the Office Action concerning the structural requirements of inhibitory agents according to the invention. The Examiner stated therein that the disclosure fails to provide adequate guidance pertaining to the structural requirements of any given inhibitor and absent any guidance concerning the structure of said compounds, an undue invitation to further experimentation has been extended to the skilled artisan. In response, applicants contend that given the four antibodies disclosed as working examples of the presently claimed invention (see Table 3), one skilled in this art could readily determine the structure of one or more of the subject antibodies

and thus produce other, related antibodies and/or antibody fragments having an inhibitory effect, as recited in the preamble of claim 7, on the fusion of a macrophage-tropic primary isolate of HIV-1 and a CD4+ cell susceptible to infection by such macrophage-tropic primary isolate of HIV-1.

Applicants additionally note the Examiner's statement in ¶4 on page 6 of the Office Action that, "the disclosure clearly illustrates the problems associated with identifying specific inhibitors wherein it was reported (page 60, first paragraph) that 'The culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 inhibited fusion between HeLa-env_{JR-F1} and PM1 cells in the RET assay, and also inhibited fusion between HeLa-env_{LAI} cells and certain CD4+ target cells (Table 3)' ". Applicants respectfully submit, however, that their claims (e.g., claim 7) are not directed to a method of inhibiting fusion between HeLa-env_{LAI} and "certain CD4+ target cells." Rather, as pointed out above, the amended claims are specifically directed to a method of inhibiting fusion which entails contacting CD4+ cells susceptible to infection by a macrophage-tropic primary isolate of HIV-1, which method specifically requires that such CD4+ cells be contacted with an agent which is (1) capable of inhibiting fusion of HeLa-env_{JR-F1} to a PM1 cell, but (2) not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. As demonstrated by the experimental results set forth in Table 3, antibodies having the requisite properties are readily obtainable by those of ordinary skill in the art based on the teachings contained in the present application. That is, the per cent inhibition values shown in Table 3 readily demonstrate that the PA-3, PA-5, PA-6 and PA-7 antibodies meet all of the requirements of claim 7 and thus the subject claim clearly is enabled. Moreover, as the remaining claims of the application (nos. 8, 9 and 13) all depend from claim 7 and thus contain all of the

recitations of the subject claim, claims 8, 9 and 13 are also enabled by applicants' specification. The Examiner is therefore respectfully requested to reconsider and withdraw the "enablement" rejection of applicants' claims under 35 U.S.C. §112, ¶1.

Summary

In view of the amendments and remarks herein, applicants respectfully request that the Examiner withdraw the rejection of the claims as set forth in the July 1, 2003 Office Action and earnestly solicit allowance of claims 7-9 and 13 which are pending in this application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone either of them at the number provided below.

A fee of Four Hundred Seventy-Five Dollars ($475.00) is deemed necessary for filing this Amendment. A check for the subject amount is enclosed herewith. If any additional fees are due, authorization is hereby given to charge the amount of such required fee(s) to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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